

Small Cell Carcinoma of the Gallbladder

THOMAS L. MOSKAL, MD,¹ PAUL J. ZHANG, MD,² AND HECTOR R. NAVA, MD^{1*}

¹*Division of Surgical Oncology, Department of Upper Gastrointestinal Surgery and Endoscopy, Roswell Park Cancer Institute, Buffalo, New York*

²*Division of Pathology, Roswell Park Cancer Institute, Buffalo, New York*

Background and Objectives: Small cell carcinoma of the gallbladder is rare with only 36 cases reported in the literature. Early reports demonstrated an extremely poor prognosis for this histologic type. Five new cases are reported and the previous experience in the literature is reviewed to further clarify the clinical behavior of this malignancy.

Methods: A retrospective analysis is performed on 5 new cases. An extensive review of the literature is also performed.

Results: Twenty-eight pure small cell carcinomas and 8 combined small cell carcinomas with adenocarcinoma are reported in the literature. Conclusions from the literature review reveal that small cell carcinoma of the gallbladder affects an elderly patient population (median age 65 years), has a female preponderance (76%), is associated with cholelithiasis (72%), metastasizes to nodes (88%), liver (88%), lung (23%), and peritoneum (19%), and has a median survival of 4 months. Pure tumors had median survivals of 9 months and combined tumors had median survivals of 4.5 months. The 5 patients in the literature treated with surgery and chemotherapy had improved median survival of 13 months. The 5 newly reported cases had similar epidemiological characteristics to the literature data, however, these cases were managed aggressively with surgery and chemotherapy, demonstrating a median survival of 31 months.

Conclusions: Although small cell carcinoma of the gallbladder is a distinct histologic and clinical entity, it has many clinical characteristics similar to adenocarcinoma of the gallbladder including comparable natural history and tendency for locoregional spread. Aggressive multimodality therapy, especially the combination of surgery and chemotherapy, may improve survival. *J. Surg. Oncol.* 1999;70:54–59. © 1999 Wiley-Liss, Inc.

KEY WORDS: gallbladder neoplasm; small cell carcinoma; neuroendocrine tumor

INTRODUCTION

Six thousand cases of gallbladder carcinoma are seen annually in the United States. Approximately 90% of these have an adenocarcinoma histology, including papillary, intestinal type, mucinous, clear cell, and signet ring variants. Other rarely seen histologic types include squamous cell, adenosquamous, undifferentiated carcinoma, carcinosarcoma, and small cell carcinoma. Small cell carcinomas are poorly differentiated neuroendocrine tumors and are associated with a poor prognosis. Thirty-six cases of small cell carcinomas have been reported in the literature with 28 pure small cell carcinomas and 8 combined tumors of small cell carcinoma and adenocar-

cinoma [1–11]. In this study, 5 new cases are reported and the literature is reviewed to further clarify this rare type of gallbladder malignancy.

MATERIALS AND METHODS

Between 1971 and 1997, 144 patients with a gallbladder malignancy were placed in a prospective tumor reg-

*Correspondence to: Hector R. Nava, MD, Department of Upper Gastrointestinal Surgery and Endoscopy, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, 14263.

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TABLE I. Summary of Patients With Small Cell Carcinoma of the Gallbladder*

Age (years)/ gender	Stage/TNM	GS	Histology	Treatment	Survival (months)
69/F	IVB/T3N2M0	—	Comb	C, S, C	44
57/F	III/T3N1M0	+	Pure	S, C, X	31
69/M	III/T2N1M0	+	Pure	s, C, X	21
71/F	IVB/T2N2M1	+	Comb	s, C, X	13
40/M	III/T2N1M0	+	Comb	s, C	189+

*TNM, tumor, node, and metastasis; GS, gallstones; Comb, combined; C, chemotherapy; S, radical surgery; X, radiation therapy; s, cholecystectomy.

istry at Roswell Park Cancer Institute. The database was searched for small cell carcinoma of the gallbladder and 5 patients were identified. A retrospective chart review was performed with clinical and pathologic assessment. Histologic materials were reviewed by one pathologist (P.J.Z.) to confirm diagnosis.

Extensive literature review of the 36 reported cases was also performed.

RESULTS

Table I describes the 5 new cases of small cell carcinoma of the gallbladder identified in our registry of 144 patients (frequency 3.5%). Three patients are female and 2 are male. Median age is 69 years, ranging from 40 to 71 years. Four patients had cholelithiasis. Four patients had a tobacco smoking history. All patients had stage III or IV disease. One patient had a functional lesion with elevated serotonin and 5-hydroxyindole acetic acid (5-HIAA) that was clinically insignificant. All patients were treated with surgery and a variety of chemotherapeutic agents. Median survival was 31 months, ranging from 13 to 189 months. Two patients had pure small cell carcinoma with survivals of 21 and 31 months. Three patients had combined small cell carcinoma with adenocarcinoma with survivals of 13, 44, and 189 months. All patients had regional nodal involvement and one patient had distant metastasis at presentation. Patients with N1 disease had survivals of 31, 21, and 189+ months. The patient with M1 disease survived 13 months. Cholecystectomy was performed in 3 patients with survivals of 13, 21, and 189 months. Radical surgery was performed in 2 patients with survivals of 31 and 44 months. The patient treated with cisplatin, etoposide, 5-fluorouracil (5-FU), doxorubicin, and mitomycin survived 44 months; with 5-FU and leucovorin survived 31 months; with streptozotocin and 5-FU survived 21 months; with 5-fluorodeoxyuridine (FUDR) and leucovorin survived 13 months; and with 5-FU survived 189 months. Sites of metastatic disease were reported for all patients as follows: nodes (n = 5), liver (n = 3), lungs (n = 3), peritoneum (n = 1), and

bone (n = 1). Three patients were treated with palliative radiation therapy.

Case 1

A 69-year-old white female non-smoker presented with chronic abdominal pain of 2 months duration, fevers, and a weight loss of 22 lb. Computed tomographic (CT) scan imaging revealed a gallbladder mass. Elevations in total bilirubin (7.6 mg/dl), lactate dehydrogenase (1083 U/l), and aspartate aminotransferase (274 U/l) were observed. Percutaneous fine-needle aspiration biopsy was suspicious for lymphoma. Staging laparotomy revealed a gallbladder mass adherent to the liver, small bowel, and omentum. Pathology on open biopsy revealed small cell carcinoma of the gallbladder.

The patient was treated with 5 cycles of cisplatin and etoposide monthly. Six months after diagnosis the patient underwent radical cholecystectomy and pancreaticoduodenectomy, because of tumor nodal involvement of the head of the pancreas. Histologic examination revealed a combined tumor of small cell carcinoma and poorly differentiated adenocarcinoma. No gallstones were seen. The patient had stage IVB, T3N2M0 disease. From 4 to 20 months postoperatively the patient was treated with 5-FU every 5 weeks. Thirty-three months after surgery the patient had intra-abdominal recurrence. The patient received one cycle of 5-FU, doxorubicin, and mitomycin with a partial response observed, but this regimen was discontinued secondary to significant toxicity. The patient died 44 months after beginning treatment with preoperative chemotherapy.

Case 2

A 57-year-old white female cigarette smoker presented with chronic abdominal pain. CT scan imaging and ultrasound revealed cholelithiasis, choledocholithiasis, and a right lobe liver mass. Elevations in total bilirubin (3.6 mg/dl), lactate dehydrogenase (448 U/l), aspartate aminotransferase (561 U/l), and alanine aminotransferase (873 U/l) were observed.

The patient was treated with right extended hepatic lobectomy and common bile duct exploration. Histologic examination revealed small cell carcinoma of the gallbladder. The patient had stage III, T3N1M0 disease. Intra-abdominal recurrence was observed 12 months postoperatively and this was treated with 5-FU and leucovorin. Twenty-four months postoperatively spine and hip bone metastasis were treated with 3,000 rads of external beam radiation therapy to each site. The patient died 31 months after surgery.

Case 3

A 69-year-old white male pipe smoker presented with a history of chronic abdominal pain. Ultrasound exami-

nation revealed cholelithiasis. No elevations in laboratory tests were seen.

The patient was treated with open cholecystectomy. Histologic examination revealed a small cell carcinoma. The patient had stage III, T2N1M0 disease. Postoperative CT scan imaging revealed retroperitoneal disease. Postoperative elevations in serotonin and 5-HIAA were observed that were clinically insignificant. Eight months postoperatively the patient began 4 cycles of streptozotocin and 5-FU for 5 days every 10 weeks. The patient had stable disease. Twenty months postoperatively the patient developed bilateral malignant pleural effusions that were treated with bleomycin pleurodesis. Twenty-one months postoperatively the retroperitoneum was treated with 3,600 rads of external beam radiation therapy. The patient died 21 months after initial operation.

Case 4

A 71-year-old white female former cigarette smoker presented with incidental gallstones demonstrated on CT scan imaging. There were no preoperative laboratory abnormalities.

The patient was treated with laparoscopic cholecystectomy. Histologic examination revealed a combined tumor of small cell carcinoma and poorly differentiated adenocarcinoma. The patient had T2NXMO disease. Postoperative CT scan imaging revealed enlarged retroperitoneal lymph nodes. One month postoperatively the patient underwent exploratory laparotomy and was found to have multiple liver capsular involvement, multiple posterior peritoneal involvement, and trocar site recurrence. At that time, wide local excision of one port site recurrence was performed. The patient was restaged as stage IVB, T2N2M1. Three months after initial surgery the patient was treated with 6 cycles of FUDR and leucovorin given weekly for 4 weeks. Seven months after initial surgery the patient received 4,500 rads of external beam radiation therapy to the retroperitoneum. The patient died 13 months after initial surgery.

Case 5

A 40-year-old white male cigarette smoker presented with a history of chronic abdominal pain. His past medical history is significant for pancreatitis with elevated bilirubin requiring Roux-en-Y cholecystojejunostomy 10 years previously.

The patient was treated with takedown of Roux-en-Y cholecystojejunostomy, cholecystectomy, and choledochoduodenostomy. Histologic examination revealed a combined tumor of small cell carcinoma and moderately differentiated adenocarcinoma. Gallstones were seen. The patient had stage III, T2N1M0 disease. The patient was treated with 5-FU for 1 year postoperatively. Fifteen years postoperatively the patient developed intra-abdominal and left lung recurrences. The left upper lobe

lung metastasis was treated with thoracoscopic wedge resection. The symptomatic abdominal recurrence was treated with en bloc resection of transverse colon, omentum, adherent jejunum, abdominal wall, and lateral left lobe of liver. Pathology of both was the same as the pathology from 15 years prior. The patient is presently alive with no evidence of disease 189 months after his first operation.

LITERATURE REVIEW

Table II describes the 36 cases of small cell carcinoma of the gallbladder previously reported in the literature [1–11]. Twenty-eight (76%) were female and 8 were male. Median age is 65 years, ranging from 37 to 82 years. Twenty-eight were pure small cell carcinomas and 8 were combined small cell carcinomas with adenocarcinoma. Twenty-six (72%) had cholelithiasis. Twenty-three reports were clinical cases and 13 reports were autopsy cases. Sites of metastatic disease were reported for 26 patients in the liver ($n = 23$), nodes ($n = 23$), lung ($n = 6$), peritoneum ($n = 5$), omentum ($n = 2$), pancreas ($n = 2$), rectum ($n = 1$), bone ($n = 1$), adrenal ($n = 1$), and ovary ($n = 1$).

For the 23 clinical cases, median age ($n = 22$) was 66.5 years, ranging from 37 to 82 years, and median survival ($n = 19$) was 4 months, ranging from 1 to 59 months. Nineteen had pure small cell tumors with median age ($n = 13$) 68 years, ranging from 37 to 82 years, and median survival of 9 months, ranging from 1 to 59 months. Four had combined small cell tumors with adenocarcinoma with median age of 70.5 years, ranging from 62 to 71 years, and median survival of 4.5 months, ranging from 1 to 20 months. The patients with reported stages ($n = 7$) had either stage III or IV disease. Thirteen (57%) had cholelithiasis. Treatment included surgery alone in 14 with a median survival of 4 months, surgery and chemotherapy in 5 with a median survival of 13 months, chemotherapy alone in 3 with survival data not reported, and no treatment in 1 patient with a survival of 1 month. Surgery was performed in 19 of the 22 treated patients with median survival of 4.5 months.

Cholecystectomy was performed in 12 with a median survival of 4.5 months, and radical resection was performed in 2 patients with survivals of 4 and 20 months. Extent of surgery was not known in 5 patients and 4 of these had survivals of 2, 2, 9, and 59 months. Chemotherapy with doxorubicin, vincristine, cyclophosphamide, and nitrosurea in 2 patients yielded survivals of 11 and 13 months; with cisplatin and etoposide in 2 patients with survivals of 18+ and 13 months; and with etoposide in 1 patient surviving 2 months. Chemotherapy type in 3 patients was not reported. Sites of metastatic disease were reported for 14 patients in the liver ($n = 13$), nodes ($n = 10$), peritoneum ($n = 3$), lungs ($n = 2$), pancreas

TABLE II. Patients With Small Cell Carcinoma of the Gallbladder in the Literature*

Age (years)/gender	Stage/TNM	GS	Histology	Treatment	Survival (months)	Ref.
55/M	NR	+	NR	None	Autopsy	[1]
72/F	NR	+	NR	None	Autopsy	[1]
74/F	NR	+	NR	None	Autopsy	[1]
65/M	NR	+	NR	s	<4	[1]
58/F	NR	+	NR	s	<4	[1]
75/F	NR	+	NR	None	Autopsy	[2]
67/F	NR	+	NR	None	Autopsy	[2]
66/F	NR	+	NR	None	Autopsy	[2]
67/F	NR	+	NR	None	Autopsy	[2]
60/F	NR	+	NR	None	Autopsy	[2]
60/F	NR	+	NR	None	Autopsy	[2]
48/F	NR	+	NR	None	Autopsy	[2]
79/F	NR	+	NR	s	<4	[2]
55/F	NR	+	NR	s, C	11	[2]
72/F	NR	+	NR	None	Autopsy	[2]
55/F	NR	+	NR	None	Autopsy	[2]
NA/F	NR	+	NR	s	<4	[2]
50/F	NR	+	NR	None	Autopsy	[2]
52/F	NR	—	NR	s, C	13	[2]
44/F	NR	—	Pure	Surg	NR	[3]
75/F	NR	—	Pure	Surg	9	[3]
72/F	NR	—	Pure	Surg	2	[3]
56/F	NR	—	Pure	Surg	2	[3]
68/F	NR	+	Pure	Surg	59+	[3]
50/F	NR	—	Pure	C	NR	[3]
69/M	NR	+	Pure	C	NR	[3]
73/M	NR	+	Pure	C	NR	[3]
72/F	NR/T2NXM0	+	Pure	s	12+	[4]
71/F	III/TXN1M0	—	Combined	S	4	[5]
70/M	IVB/T2N2M1	—	Combined	None	1	[6]
62/F	IVA/T3NXM0	—	Combined	s	5	[7]
60/M	IVB/TXN2M1	+	Pure	s, C	18+	[8]
61/M	NR/T2NXM0	+	Pure	s, C	2	[9]
71/F	III/TXN1M0	+	Combined	S	20	[10]
37/F	IVA/T3NXM0	—	Pure	s, C	13	[11]
82/M	IVB/TXN2M1	+	Pure	s	<1	[11]

* TNM, tumor, node, and metastasis; GS, gallstones; NR, not reported; C, chemotherapy; S, radical surgery; s, cholecystectomy; Surg, extent of surgery not reported.

(n = 2), omentum (n = 1), rectum (n = 1), and adrenal (n = 1). None of the patients received radiation therapy.

DISCUSSION

More than 90% of gallbladder malignancies are adenocarcinomas, however, a variety of neuroendocrine tumors of the gallbladder have been described [1–12]. The neuroendocrine nature of these tumors has been firmly established with electron microscopy and immunohistochemical staining. Normal lung contains neuroendocrine cells and small cell carcinoma is common in the lung, accounting for approximately 20% of all lung cancers [13]. Normal gallbladder does not contain neuroendocrine cells and thus these tumors are very rare. Neuroendocrine cells have been shown in mucosal metaplasia, often seen accompanying cholelithiasis and cholecystitis [14,15]. With immunohistochemical staining neuroendo-

crine cells have also been identified in gallbladder adenocarcinoma [16]. The histogenesis of small cell carcinoma is currently believed to be of epithelial origin [17,18]. Small cell carcinoma and carcinoid represent, respectively, the poorly differentiated and well-differentiated spectrum of neuroendocrine tumors [19].

Approximately 40,000 pulmonary and 1,000 extrapulmonary cases of small cell carcinoma occur annually in the United States [20]. For extrapulmonary sites the gastrointestinal tract accounts for 35% of cases usually occurring in the colorectum, esophagus, and pancreas; the head and neck area accounts for 27% of cases usually occurring in the salivary glands, sinuses, and larynx; the genitourinary system accounts for 15% of cases usually occurring in the bladder and prostate; the gynecologic system accounts for 12% of cases usually occurring in the cervix; and other areas account for 11% of cases [21].

Thirty-six cases of small cell carcinoma of the gallbladder are reported in the literature [1–11]. The incidence of 3.5% seen in our series coincides with those reported by other referral center hospitals [2]. Surveillance, Epidemiology, and End Results (SEER) data reveal the incidence to be closer to 0.5%, accounting for 30 cases annually [12]. The histopathologic classification of small cell lung cancer reveals that 92.8% are pure tumors, 4% are mixed small cell and large cell, and 3.2% are combined small cell and adenocarcinoma or squamous cell carcinoma [22]. For gallbladder small cell carcinoma, 28 (78%) pure small cell carcinoma and 8 (22%) combined small cell carcinoma and adenocarcinoma are reported in the literature. In our series, 2 pure tumors and 3 combined tumors were seen. The prognostic significance of histopathologic subtype of small cell carcinoma remains to be defined. In 1992, Friare et al. [22] described similar survival for pure and combined tumors of the lung. In the literature, the pure gallbladder tumors had increased survival, while in the 5 newly reported cases survival was equally good between the two groups. Functionality of small cell carcinoma is frequently reported. Functionality in gallbladder sites is not commonly reported and in our literature review none of the patients had function reported and it is probable that functional status was not assessed. One of the newly reported patients had clinically insignificant elevations in serotonin and 5-HIAA, while function in the other 4 patients was not assessed. At this time, assessment of functionality is recommended to further define its role in gallbladder small cell carcinoma.

Cigarette smoking has been recognized as the most significant risk factor for lung small cell carcinoma, which affects males and females in a 2 to 1 ratio. Pulmonary small cell carcinoma presents with distant disease 70% of the time to bone, liver, brain, and nodes [13]. Treatment of pulmonary small cell lung carcinoma centers on chemotherapy with good responses with such regimens as cisplatin and etoposide [13,23]. Surgery for early disease and radiation of thorax and cranium are used in certain situations. Because 5-year overall survivals are approximately 5%, new therapies are being investigated. Treatment patterns for extrapulmonary small cell carcinoma have tended to follow treatment patterns for pulmonary small cell carcinoma [24]. However, the natural history and treatment responses of small cell carcinomas at different organ sites can be variable [17]. In our literature review of gallbladder small cell carcinoma, 76% of the patients were female, risk factors were not reported, and metastasis history was predominantly local to nodes and liver. Cholecystectomy was the main treatment with a poor median survival of 4.5 months. The 5 patients in the literature treated with cholecystectomy followed by chemotherapy showed an increased median survival of 13 months. In the 5 newly reported cases,

60% were female, 80% had a tobacco smoking history, and metastasis history was predominantly to nodes, liver, and lung. All 5 patients were treated with surgery and chemotherapy with a good median survival of 31 months.

From our literature review it is clear that small cell carcinoma of the gallbladder has many similarities with adenocarcinoma of the gallbladder. They both affect an older patient population, have a female preponderance, involve cholelithiasis, often present with late stage disease, have a tendency for locoregional spread to liver, nodes, peritoneum, and lungs, and have a poor prognosis. Standard treatment of gallbladder adenocarcinoma relies strongly on surgical resection with the roles of radiation therapy and chemotherapy not clearly defined [25]. The role of surgery in the treatment of gallbladder carcinoma including radical surgery remains controversial [25,26]. In the literature, stage information was frequently not reported and treatments were often not aggressive, consisting of cholecystectomy alone followed by chemotherapy regimens typically used in the treatment of pulmonary small cell cancer with a median survival of 4 months. In the 5 newly presented cases, the patients were managed with multimodality treatment with surgery and chemotherapy regimens not typically used in the treatment of lung small cell carcinoma with median survival of 31 months. Two of these patients were treated with radical surgery including right extended hepatic lobectomy and pancreaticoduodenectomy with survival of 31 and 44 months. None of the patients received radiation therapy adjuvantly, but 3 were treated with palliative radiation therapy.

Standard chemotherapy treatment regimens for pulmonary small cell carcinoma include cisplatin, etoposide, cyclophosphamide, doxorubicin, methotrexate, and vincristine [13,24]. 5-FU is not commonly used because of low response rates. 5-FU is commonly used in the treatment of gallbladder adenocarcinoma [25]. 5-FU, streptozotocin, leucovorin, doxorubicin, cisplatin, and etoposide are successful treatments for gastrointestinal neuroendocrine tumors [27,28]. In 1989, Morant and Bruckner [29] reported a pancreatic small cell carcinoma unresponsive to combination chemotherapy including 5-FU and streptozotocin which went on to respond to cisplatin and etoposide. In 1993, Ohtsu et al. [30] reported the treatment of esophageal small cell carcinoma with 5-FU and cisplatin and radiation. In 1995, Ng et al. [31] described a patient with locally advanced esophageal small cell carcinoma treated with neoadjuvant cisplatin and 5-FU followed by surgery with survival over 16 months. Kumegawa et al. [32] reported a similar case of esophageal small cell carcinoma treated with neoadjuvant cisplatin and 5-FU and surgery with recurrence seen within 12 months. In the literature review, treatment with cisplatin and etoposide demonstrated increased survivals. In the newly reported cases, one patient was treated with neo-

adjuvant cisplatin and etoposide followed by surgery followed by 5-FU, doxorubicin, and mitomycin with good downstaging and survival. The other 4 patients were treated with 5-FU-based regimens and some with leucovorin or streptozotocin with good survivals.

Chemotherapy utilizing 5-FU, leucovorin, streptozotocin, doxorubicin, cisplatin, and etoposide plays a role in the treatment of gallbladder small cell carcinoma. Surgery is also an important element in the treatment of gallbladder small cell carcinoma where local disease is a concern, in contrast to lung small cell carcinoma where the disease is often systemic and surgery offers little benefit. Because patients often present with locally advanced late stage disease in gallbladder small cell carcinoma, neoadjuvant protocols appear to be attractive treatment alternatives.

CONCLUSIONS

Small cell carcinoma of the gallbladder is a rare malignancy with 41 cases now reported in the literature. Clinical behavior includes involvement of an elderly patient population, a female preponderance, an association with cholelithiasis, and metastasis to nodes, liver, lung, and peritoneum. This clinical picture appears more like gallbladder adenocarcinoma than pulmonary small cell carcinoma. Surgery remains the mainstay treatment, but it is apparent that patients benefit from chemotherapy regimens typically used in the treatment of gallbladder adenocarcinoma, gastrointestinal neuroendocrine tumors, and pulmonary small cell carcinoma. The role of radiation therapy has not been tested, but may prove to be useful as adjuvant therapy for local control. The previously reported dismal prognosis of small cell carcinoma of the gallbladder may no longer hold true, with improved survival being reported with multimodality treatment.

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